

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
 US Department of Commerce
 United States Patent and Trademark
 Office, PCT
 2011 South Clark Place Room
 CP2/5C24
 Arlington, VA 22202
 ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

| | |
|--|--|
| Date of mailing (day/month/year) 20 March 2001 (20.03.01) | Applicant's or agent's file reference AP/P32330 |
| International application No. PCT/EP00/05672 | Priority date (day/month/year) 18 June 1999 (18.06.99) |
| International filing date (day/month/year) 16 June 2000 (16.06.00) | |
| Applicant FARINA, Carlo et al | |

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:13 December 2000 (13.12.00)☐ in a notice effecting later election filed with the International Bureau on:2. The election ☒ was☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

| | |
|--|--|
| The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland | Authorized officer Pascal Piriou |
| Facsimile No.: (41-22) 740.14.35 | Telephone No.: (41-22) 338.83.38 |

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

RUTTER, Keith
SmithKline Beecham
Two New Horizons Court
Brentford
Middlesex TW8 9EP
ROYAUME-UNI

| | |
|--|---|
| Date of mailing (day/month/year) 29 January 2002 (29.01.02) | IMPORTANT NOTIFICATION |
| Applicant's or agent's file reference AP/P32330 | |
| International application No. PCT/EP00/05672 | International filing date (day/month/year) 16 June 2000 (16.06.00) |

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

| | | |
|--|----------------------------|--------------------------|
| Name and Address FARINA, Carlo SmithKline Beecham S.p.A. Via Zambelletti I-20021 Baranzate di Bollate Italy | State of Nationality IT | State of Residence IT |
| | Telephone No. | |
| | Facsimile No. | |
| | Teleprinter No. | |

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

| | | |
|--|----------------------------|--------------------------|
| Name and Address FARINA, Carlo Nikem Research S.r.L. Via Zambelletti, 25 I-20021 Baranzate di Bollate Italy | State of Nationality IT | State of Residence IT |
| | Telephone No. | |
| | Facsimile No. | |
| | Teleprinter No. | |

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office ☐ the designated Offices concerned
☐ the International Searching Authority ☒ the elected Offices concerned
☒ the International Preliminary Examining Authority ☐ other:

| | |
|---|--|
| The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35 | Authorized officer Simin Baharlou Telephone No.: (41-22) 338.83.38 |
|---|--|

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1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

| | | |
|--|----------------------------|--------------------------|
| Name and Address GAGLIARDI, Stefania SmithKline Beecham S.p.A. Via Zambelletti I-20021 Baranzate di Bollate Italy | State of Nationality IT | State of Residence IT |
| | Telephone No. | |
| | Facsimile No. | |
| | Teleprinter No. | |

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| | Telephone No. | |
| | Facsimile No. | |
| | Teleprinter No. | |

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4. A copy of this notification has been sent to:

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☐ the International Searching Authority ☒ the elected Offices concerned
☒ the International Preliminary Examining Authority ☐ other:

| | |
|--|---|
| <p>The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland</p> <p>Facsimile No.: (41-22) 740.14.35</p> | <p>Authorized officer Simin Baharlou</p> <p>Telephone No.: (41-22) 338.83.38</p> |
|--|---|

PATENT COOPERATION TREATY

10/018443

PCT

From the INTERNATIONAL BUREAU

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

To:

RUTTER, Keith
SmithKline Beecham
Two New Horizons Court
Brentford
Middlesex TW8 9EP
ROYAUME-UNI

RECEIVED

MAY 10 2002

TECH CENTER 1600/2900

| | |
|--|---|
| Date of mailing (day/month/year) 29 January 2002 (29.01.02) | IMPORTANT NOTIFICATION |
| Applicant's or agent's file reference AP/P32330 | |
| International application No. PCT/EP00/05672 | International filing date (day/month/year) 16 June 2000 (16.06.00) |

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

| | | |
|--|----------------------------|--------------------------|
| Name and Address NOVELLA, Pietro, A., T. SmithKline Beecham S.p.A. Via Zambelletti I-20021 Baranzate di Bollate Italy | State of Nationality IT | State of Residence IT |
| | Telephone No. | |
| | Facsimile No. | |
| | Teleprinter No. | |

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

| | | |
|--|----------------------------|--------------------------|
| Name and Address NOVELLA, Pietro, A., T. Nikem Research S.r.L. Via Zambelletti, 25 I-20021 Baranzate di Bollate Italy | State of Nationality IT | State of Residence IT |
| | Telephone No. | |
| | Facsimile No. | |
| | Teleprinter No. | |

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

| | |
|---|---|
| <input checked="" type="checkbox"/> the receiving Office | <input type="checkbox"/> the designated Offices concerned |
| <input type="checkbox"/> the International Searching Authority | <input checked="" type="checkbox"/> the elected Offices concerned |
| <input checked="" type="checkbox"/> the International Preliminary Examining Authority | <input type="checkbox"/> other: |

| | |
|---|--|
| The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland | Authorized officer Simin Baharlou |
| Facsimile No.: (41-22) 740.14.35 | Telephone No.: (41-22) 338.83.38 |

(19) World Intellectual Property Organization
International Bureau



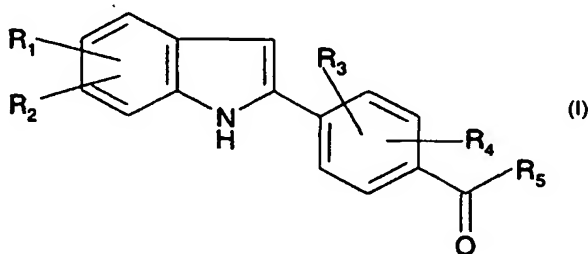
(43) International Publication Date
11 January 2001 (11.01.2001)

PCT

(10) International Publication Number
WO 01/02388 A1

- (51) International Patent Classification⁷: C07D 401/12, A61K 31/404, A61P 19/10, C07D 209/18, 403/12
- (74) Agent: RUTTER, Keith; SmithKline Beecham, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).
- (21) International Application Number: PCT/EP00/05672
- (22) International Filing Date: 16 June 2000 (16.06.2000)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
9914371.1 18 June 1999 (18.06.1999) GB
- (71) Applicant (for all designated States except US):
SMITHKLINE BEECHAM S.p.A. [IT/IT]; Via Zambelletti, I-20021 Baranzate di Bollate (IT).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): FARINA, Carlo [IT/IT]; SmithKline Beecham S.p.A., Via Zambelletti, I-20021 Baranzate di Bollate (IT). GAGLIARDI, Stefania [IT/IT]; SmithKline Beecham S.p.A., Via Zambelletti, I-20021 Baranzate di Bollate (IT). NOVELLA, Pietro, A., T. [IT/IT]; SmithKline Beecham S.p.A., Via Zambelletti, I-20021 Baranzate di Bollate (IT).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- Published:**
- With international search report.
 - Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: INDOLE DERIVATIVES AND THEIR USE FOR THE TREATMENT OF OSTEOPOROSIS AMONGST OTHER APPLICATIONS



(57) Abstract: A compound of formula (I) or a salt thereof, or a solvate thereof, wherein: R₁ and R₂ each independently represents C₁₋₆alkoxy or halo; R₃ and R₄ each independently represents hydrogen, C₁₋₆alkoxy, arylC₁₋₆alkoxy, hydroxy, carboxyC₁₋₆alkoxy, hydroxyC₁₋₆alkoxy, dihydroxyC₁₋₆alkoxy, mono- and di-(C₁₋₆alkyl)aminoC₁₋₆alkoxy or aminoC₁₋₆alkoxy, and R₅ represents -NR₅R₆ wherein R₅ and R₆ each independently represent hydrogen, unsubstituted or substituted C₁₋₆alkyl, or unsubstituted or substituted heterocyclyl, a process for the preparation of such a compound, a pharmaceutical composition containing such a compound and the use

of the compound or composition in medicine. Particular indole compounds are selective for mammalian osteoclasts, acting to selectively inhibit their bone resorbing activity. These compounds are therefore considered to be particularly useful for the treatment and/or prophylaxis of diseases associated with loss of bone mass, such as osteoporosis and related osteopenic diseases, Paget's disease, hyperparathyroidism and related diseases. These compounds are also considered to possess antitumour activity, antiviral activity (for example against *Semliki Forest*, *Vesicular Stomatitis*, *Newcastle Disease*, *Influenza A* and *B*, *HIV* viruses), antiulcer activity (for example the compounds may be useful for the treatment of chronic gastritis and peptic ulcer induced by *Helicobacter pylori*) immunosuppressant activity, antilipidemic activity, antiatherosclerotic activity and to be useful for the treatment of AIDS and Alzheimer's disease. Furthermore, these compounds are also considered useful in inhibiting angiogenesis i.e. the formation of new blood vessels which is observed in various types of pathological conditions (*angiogenic diseases*) such as rheumatoid arthritis, diabetic retinopathy, psoriasis and solid tumours.

INTERNATIONAL SEARCH REPORT

Application No
PCT/00/05672

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D401/12 A61K31/404 A61P19/10 C07D209/18 C07D403/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| A | WO 98 01443 A (SMITHKLINE BEECHAM S.P.A.) 15 January 1998 (1998-01-15) claims | 1,2, 22-29 |
| A | WO 96 21644 A (SMITHKLINE BEECHAM S.P.A.) 18 July 1996 (1996-07-18) claims | 1,2, 22-29 |
| P,X | WO 99 33822 A (SMITHKLINE BEECHAM LABORATOIRES PHARMACEUTIQUES) 8 July 1999 (1999-07-08) * complete document * | 1-5,15, 22-29 |

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- * & * document member of the same patent family

Date of the actual completion of the international search

6 November 2000

Date of mailing of the international search report

28/11/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Van Bijlen, H

INTERNATIONAL SEARCH REPORT

Information on patent family members

Application No
PCT/00/05672

| Patent document cited in search report | | Publication date | Patent family member(s) | Publication date |
|---|---|---------------------|----------------------------|---------------------|
| WO 9801443 | A | 15-01-1998 | AU 3620597 A | 02-02-1998 |
| | | | BR 9710230 A | 10-08-1999 |
| | | | CA 2259598 A | 15-01-1998 |
| | | | CZ 9900037 A | 11-08-1999 |
| | | | EP 0914321 A | 12-05-1999 |
| | | | NO 990080 A | 08-01-1999 |
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| | | | ZA 9706064 A | 08-02-1999 |
| WO 9621644 | A | 18-07-1996 | IT MI950030 A | 10-07-1996 |
| | | | IT MI951687 A | 03-02-1997 |
| | | | AP 648 A | 25-05-1998 |
| | | | AU 4536096 A | 31-07-1996 |
| | | | BG 101769 A | 30-04-1998 |
| | | | BR 9606743 A | 30-12-1997 |
| | | | CA 2209936 A | 18-07-1996 |
| | | | CZ 9702176 A | 18-03-1998 |
| | | | EP 0802902 A | 29-10-1997 |
| | | | FI 972919 A | 09-09-1997 |
| | | | HU 9901096 A | 28-07-1999 |
| | | | JP 10512251 T | 24-11-1998 |
| | | | NO 973178 A | 09-09-1997 |
| | | | PL 321263 A | 24-11-1997 |
| | | | SK 93297 A | 04-02-1998 |
| | | | US 5981525 A | 09-11-1999 |
| WO 9933822 | A | 08-07-1999 | AU 2715499 A | 19-07-1999 |
| | | | BR 9814403 A | 10-10-2000 |
| | | | EP 1042316 A | 11-10-2000 |
| | | | NO 20003315 A | 23-06-2000 |

PA T COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| | | |
|---|---|--|
| Applicant's or agent's file reference AP/P32330 | FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below. | |
| International application No. PCT/EP 00/ 05672 | International filing date (day/month/year) 16/06/2000 | (Earliest) Priority Date (day/month/year) 18/06/1999 |
| Applicant SMITHKLINE BEECHAM S.P.A. | | |

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.



the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :



contained in the international application in written form.



filed together with the international application in computer readable form.



furnished subsequently to this Authority in written form.



furnished subsequently to this Authority in computer readable form.



the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.



the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,



the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

INDOLE DERIVATIVES AND THEIR USE FOR THE TREATMENT OF OSTEOPOROSIS AMONGST OTHER APPLICATIONS

5. With regard to the **abstract**,



the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.



as suggested by the applicant.



because the applicant failed to suggest a figure.



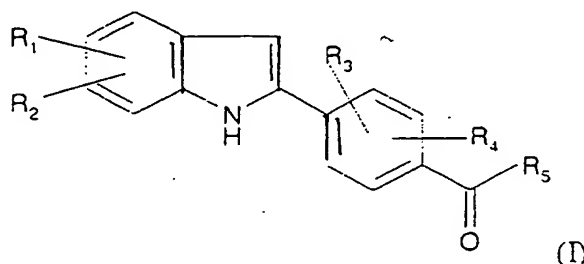
because this figure better characterizes the invention.



None of the figures.

Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)

A compound of formula (I)



or a salt thereof, or a solvate thereof,
wherein;

R_1 and R_2 each independently represents C_{1-6} alkoxy or halo;

R_3 and R_4 each independently represents hydrogen, C_{1-6} alkoxy, aryl C_{1-6} alkoxy, hydroxy, carboxy C_{1-6} alkoxy, hydroxy C_{1-6} alkoxy, dihydroxy C_{1-6} alkoxy, mono- and di- $(C_{1-6}$ alkyl)amino C_{1-6} alkoxy or amino C_{1-6} alkoxy, and;

R_5 represents $-NR_5R_t$ wherein R_5 and R_t each independently represent hydrogen, unsubstituted or substituted C_{1-6} alkyl, or unsubstituted or substituted heterocyclyl, a process for the preparation of such a compound, a pharmaceutical composition containing such a compound and the use of the compound or composition in medicine.

Particular indole compounds are selective

for mammalian osteoclasts, acting to selectively inhibit their bone resorbing activity. These compounds are therefore considered to be particularly useful for the treatment and/or prophylaxis of diseases associated with loss of bone mass, such as osteoporosis and related osteopenic diseases, Paget's disease, hyperparathyroidism and related diseases. These compounds are also considered to possess antitumour activity, antiviral activity (for example against *Semliki Forest*, *Vesicular Stomatitis*, *Newcastle Disease*, *Influenza A* and *B*, *HIV* viruses), antiulcer activity (for example the compounds may be useful for the treatment of chronic gastritis and peptic ulcer induced by *Helicobacter pylori*), immunosuppressant activity, antilipidemic activity, antiatherosclerotic activity and to be useful for the treatment of AIDS and Alzheimer's disease. Furthermore, these compounds are also considered useful in inhibiting angiogenesis i.e. the formation of new blood vessels which is observed in various types of pathological conditions (*angiogenic diseases*) such as rheumatoid arthritis, diabetic retinopathy, psoriasis and solid tumours.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/00/05672

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D401/12 A61K31/404 A61P19/10 C07D209/18 C07D403/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| A | WO 98 01443 A (SMITHKLINE BEECHAM S.P.A.) 15 January 1998 (1998-01-15) claims --- | 1,2, 22-29 |
| A | WO 96 21644 A (SMITHKLINE BEECHAM S.P.A.) 18 July 1996 (1996-07-18) claims --- | 1,2, 22-29 |
| P,X | WO 99 33822 A (SMITHKLINE BEECHAM LABORATOIRES PHARMACEUTIQUES) 8 July 1999 (1999-07-08) * complete document * ----- | 1-5,15, 22-29 |

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

6 November 2000

Date of mailing of the international search report

28/11/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Van Bijlen, H

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

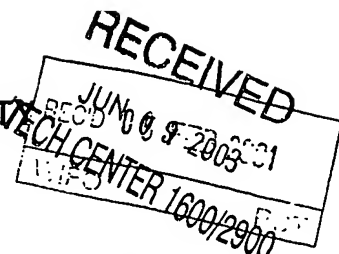
PCT. 00/05672

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---------------------|---|--|
| WO 9801443 A | 15-01-1998 | AU 3620597 A BR 9710230 A CA 2259598 A CZ 9900037 A EP 0914321 A NO 990080 A PL 330994 A ZA 9706064 A | 02-02-1998 10-08-1999 15-01-1998 11-08-1999 12-05-1999 08-01-1999 21-06-1999 08-02-1999 |
| WO 9621644 A | 18-07-1996 | IT MI950030 A IT MI951687 A AP 648 A AU 4536096 A BG 101769 A BR 9606743 A CA 2209936 A CZ 9702176 A EP 0802902 A FI 972919 A HU 9901096 A JP 10512251 T NO 973178 A PL 321263 A SK 93297 A US 5981525 A | 10-07-1996 03-02-1997 25-05-1998 31-07-1996 30-04-1998 30-12-1997 18-07-1996 18-03-1998 29-10-1997 09-09-1997 28-07-1999 24-11-1998 09-09-1997 24-11-1997 04-02-1998 09-11-1999 |
| WO 9933822 A | 08-07-1999 | AU 2715499 A BR 9814403 A EP 1042316 A NO 20003315 A | 19-07-1999 10-10-2000 11-10-2000 23-06-2000 |

10/018443

PATENT COOPERATION TREATY

PCT



INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| | | |
|--|--|--|
| Applicant's or agent's file reference AP/FR/P32330 | FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) | |
| International application No. PCT/EP00/05672 | International filing date (day/month/year) 16/06/2000 | Priority date (day/month/year) 18/06/1999 |
| International Patent Classification (IPC) or national classification and IPC C07D401/12 | | |
| Applicant SMITHKLINE BEECHAM S.P.A. et al. | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 7 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

| | |
|---|--|
| Date of submission of the demand 13/12/2000 | Date of completion of this report 01.02.2001 |
| Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465 | Authorized officer Stroeter, T  |

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP00/05672

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).):*

Description, pages:

1-38 as originally filed

Claims, No.:

1-29 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP00/05672

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 19-21.

because:

☒ the said international application, or the said claims Nos. 19-21 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N) Yes: Claims 1-29
 No: Claims

Inventive step (IS) Yes: Claims 1-29
 No: Claims

Industrial applicability (IA) Yes: Claims 1-29

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP00/05672

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 19 to 21 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT). Related claims 27 to 29, however, do fulfil said requirements.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Prior art documents

Reference is made to the following documents. The given numbering will be adhered to in the rest of the procedure:

D1: WO 98 01443 A (SMITHKLINE BEECHAM S.P.A.) 15 January 1998 (1998-01-15)

D2: WO 96 21644 A (SMITHKLINE BEECHAM S.P.A.) 18 July 1996 (1996-07-18)

D3: WO 99 33822 A (SMITHKLINE BEECHAM LABORATOIRES PHARMACEUTIQUES) 8 July 1999 (1999-07-08)

D1 to D3 reveal compounds which inhibit the bone resorbing activity of osteoclasts. Concerning D3 please also see section VI.

2 Novelty (Article 33(2) PCT) and Inventive step (Article 33(3) PCT)

Article 33(2) PCT: D1 and D2 reveal compounds which inhibit the bone resorbing activity of osteoclasts. The group of compounds as claimed in present **claim 1** (as well as in dependent **claims 2 to 17**) is novel over D1 and D2 due to the absence of the grouping R_b as the most distinguishing feature.

Article 33(3) PCT: By revealing such compounds of formula (I), the present application gives a non-obvious solution to the problem of how to provide alternative compounds which show said activity. It takes various structural modifications to arrive at the present compounds when starting from the compounds of the closest prior art documents D1 and D2 and therefore it could not be foreseen by the skilled man that the presently claimed compounds are active as described.

Thus, present product claims 1 to 17 and corresponding claims 18 to 29 are novel and inventive according to Art. 33(2) and (3) PCT.

3 Industrial applicability (Article 33(4) PCT)

The subject-matter of the present **claims 1 to 18 and 22 to 29** is in accordance with the requirements of Article 33(4) PCT.

For the assessment of the present **claims 19 to 21** on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP00/05672

No: Claims

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP00/05672

Re Item VI

Certain documents cited

The International Search Report mentions one P-document D3, which does not form part of the state of the art according to Rule 64.1(b) PCT. For the purposes of this communication the priorities of the present application and the above prior art have not been checked and it has been assumed that they are valid. The Applicant is informed, that D3 discloses subject-matter that is comprised in the scope of the present set of claims.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)

To:

SMITHKLINE BEECHAM
Attn. RUTTER, Keith
Two New Horizons Court
Brentford
Middlesex TW8 9EP
UNITED KINGDOM

Date of mailing
(day/month/year)

28/11/2000

Applicant's or agent's file reference

AP/P32330

FOR FURTHER ACTION

See paragraphs 1 and 4 below

International application No.

PCT/EP 00/ 05672

International filing date
(day/month/year)

16/06/2000

Applicant

SMITHKLINE BEECHAM S.P.A.

1. ☒ The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority



European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

John De Bruijn

NOTES FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| | | | |
|---|---|--|---|
| Applicant's or agent's file reference AP/P32330 | FOR FURTHER ACTION | | see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below. |
| International application No. PCT/EP 00/ 05672 | International filing date (day/month/year) 16/06/2000 | (Earliest) Priority Date (day/month/year) 18/06/1999 | |
| Applicant SMITHKLINE BEECHAM S.P.A. | | | |

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.



the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :



contained in the international application in written form.



filed together with the international application in computer readable form.



furnished subsequently to this Authority in written form.



furnished subsequently to this Authority in computer readable form.



the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.



the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,



the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

INDOLE DERIVATIVES AND THEIR USE FOR THE TREATMENT OF OSTEOPOROSIS AMONGST OTHER APPLICATIONS

5. With regard to the **abstract**,



the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.



as suggested by the applicant.



because the applicant failed to suggest a figure.



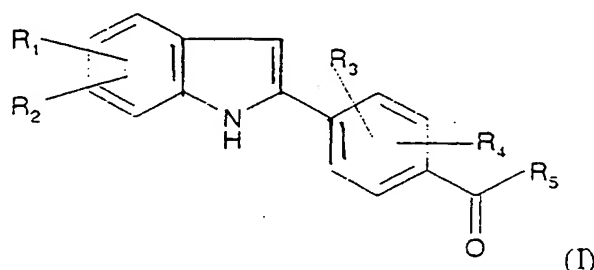
because this figure better characterizes the invention.



None of the figures.

Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)

A compound of formula (I)



or a salt thereof, or a solvate thereof,
wherein;

R_1 and R_2 each independently represents C_{1-6} alkoxy or halo;

R_3 and R_4 each independently represents hydrogen, C_{1-6} alkoxy, aryl C_{1-6} alkoxy, hydroxy, carboxy C_{1-6} alkoxy, hydroxy C_{1-6} alkoxy, dihydroxy C_{1-6} alkoxy, mono- and di- $(C_{1-6}$ alkyl)amino C_{1-6} alkoxy or amino C_{1-6} alkoxy, and;

R_5 represents $-NR_5R_t$ wherein R_5 and R_t each independently represent hydrogen, unsubstituted or substituted C_{1-6} alkyl, or unsubstituted or substituted heterocyclyl, a process for the preparation of such a compound, a pharmaceutical composition containing such a compound and the use of the compound or composition in medicine.

Particular indole compounds are selective

for mammalian osteoclasts, acting to selectively inhibit their bone resorbing activity. These compounds are therefore considered to be particularly useful for the treatment and/or prophylaxis of diseases associated with loss of bone mass, such as osteoporosis and related osteopenic diseases, Paget's disease, hyperparathyroidism and related diseases. These compounds are also considered to possess antitumour activity, antiviral activity (for example against *Semliki Forest*, *Vesicular Stomatitis*, *Newcastle Disease*, *Influenza A* and *B*, *HIV* viruses), antiulcer activity (for example the compounds may be useful for the treatment of chronic gastritis and peptic ulcer induced by *Helicobacter pylori*), immunosuppressant activity, antilipidemic activity, antiatherosclerotic activity and to be useful for the treatment of AIDS and Alzheimer's disease. Furthermore, these compounds are also considered useful in inhibiting angiogenesis i.e. the formation of new blood vessels which is observed in various types of pathological conditions (*angiogenic diseases*) such as rheumatoid arthritis, diabetic retinopathy, psoriasis and solid tumours.

INTERNATIONAL SEARCH REPORT

International Application No

PCT 00/05672

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D401/12 A61K31/404 A61P19/10 C07D209/18 C07D403/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| A | WO 98 01443 A (SMITHKLINE BEECHAM S.P.A.) 15 January 1998 (1998-01-15) claims | 1,2, 22-29 |
| A | WO 96 21644 A (SMITHKLINE BEECHAM S.P.A.) 18 July 1996 (1996-07-18) claims | 1,2, 22-29 |
| P, X | WO 99 33822 A (SMITHKLINE BEECHAM LABORATOIRES PHARMACEUTIQUES) 8 July 1999 (1999-07-08) * complete document * | 1-5,15, 22-29 |

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

° Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

6 November 2000

Date of mailing of the international search report

28/11/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Van Bijlen, H

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 00/05672

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 19-21 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

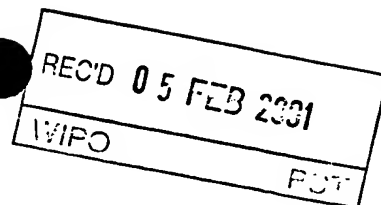
INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PC 00/05672

| Patent document cited in search report | | Publication date | Patent family member(s) | Publication date |
|---|---|---------------------|---|--|
| WO 9801443 | A | 15-01-1998 | AU 3620597 A BR 9710230 A CA 2259598 A CZ 9900037 A EP 0914321 A NO 990080 A PL 330994 A ZA 9706064 A | 02-02-1998 10-08-1999 15-01-1998 11-08-1999 12-05-1999 08-01-1999 21-06-1999 08-02-1999 |
| WO 9621644 | A | 18-07-1996 | IT MI950030 A IT MI951687 A AP 648 A AU 4536096 A BG 101769 A BR 9606743 A CA 2209936 A CZ 9702176 A EP 0802902 A FI 972919 A HU 9901096 A JP 10512251 T NO 973178 A PL 321263 A SK 93297 A US 5981525 A | 10-07-1996 03-02-1997 25-05-1998 31-07-1996 30-04-1998 30-12-1997 18-07-1996 18-03-1998 29-10-1997 09-09-1997 28-07-1999 24-11-1998 09-09-1997 24-11-1997 04-02-1998 09-11-1999 |
| WO 9933822 | A | 08-07-1999 | AU 2715499 A BR 9814403 A EP 1042316 A NO 20003315 A | 19-07-1999 10-10-2000 11-10-2000 23-06-2000 |



INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| | | |
|---|---|---|
| Applicant's or agent's file reference AP/FR/P32330 | FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) | |
| International application No. PCT/EP00/05672 | International filing date (day/month/year) 16/06/2000 | Priority date (day/month/year) 18/06/1999 |
| International Patent Classification (IPC) or national classification and IPC C07D401/12 | | |
| Applicant SMITHKLINE BEECHAM S.P.A. et al. | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 7 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

| | |
|--|---|
| Date of submission of the demand 13/12/2000 | Date of completion of this report 01.02.2001 |
| Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465 | Authorized officer Stroeter, T Telephone No. +49 89 2399 8088  |

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/05672

I. Basis of this report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).):*

Description, pages:

1-38 as originally filed

Claims, No.:

1-29 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
 - ☐ the language of publication of the international application (under Rule 48.3(b)).
 - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).
3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:
- ☐ contained in the international application in written form.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority in written form.
 - ☐ furnished subsequently to this Authority in computer readable form.
 - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
 - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/05672

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 19-21.

because:

☒ the said international application, or the said claims Nos. 19-21 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | | |
|-------------|------|--------|------|
| Novelty (N) | Yes: | Claims | 1-29 |
| | No: | Claims | |

| | | | |
|---------------------|------|--------|------|
| Inventive step (IS) | Yes: | Claims | 1-29 |
| | No: | Claims | |

| | | | |
|-------------------------------|------|--------|------|
| Industrial applicability (IA) | Yes: | Claims | 1-29 |
|-------------------------------|------|--------|------|

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP00/05672

No: Claims

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP00/05672

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 19 to 21 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT). Related claims 27 to 29, however, do fulfil said requirements.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Prior art documents

Reference is made to the following documents. The given numbering will be adhered to in the rest of the procedure:

D1: WO 98 01443 A (SMITHKLINE BEECHAM S.P.A.) 15 January 1998 (1998-01-15)

D2: WO 96 21644 A (SMITHKLINE BEECHAM S.P.A.) 18 July 1996 (1996-07-18)

D3: WO 99 33822 A (SMITHKLINE BEECHAM LABORATOIRES PHARMACEUTIQUES) 8 July 1999 (1999-07-08)

D1 to D3 reveal compounds which inhibit the bone resorbing activity of osteoclasts. Concerning D3 please also see section VI.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP00/05672

2 Novelty (Article 33(2) PCT) and Inventive step (Article 33(3) PCT)

Article 33(2) PCT: D1 and D2 reveal compounds which inhibit the bone resorbing activity of osteoclasts. The group of compounds as claimed in present **claim 1** (as well as in dependent **claims 2 to 17**) is novel over D1 and D2 due to the absence of the grouping R_b as the most distinguishing feature.

Article 33(3) PCT: By revealing such compounds of formula (I), the present application gives a non-obvious solution to the problem of how to provide alternative compounds which show said activity. It takes various structural modifications to arrive at the present compounds when starting from the compounds of the closest prior art documents D1 and D2 and therefore it could not be foreseen by the skilled man that the presently claimed compounds are active as described.

Thus, present product claims 1 to 17 and corresponding claims 18 to 29 are novel and inventive according to Art. 33(2) and (3) PCT.

3 Industrial applicability (Article 33(4) PCT)

The subject-matter of the present **claims 1 to 18 and 22 to 29** is in accordance with the requirements of Article 33(4) PCT.

For the assessment of the present **claims 19 to 21** on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP00/05672

R It m VI

Certain documents cited

The International Search Report mentions one P-document D3, which does not form part of the state of the art according to Rule 64.1(b) PCT. For the purposes of this communication the priorities of the present application and the above prior art have not been checked and it has been assumed that they are valid. The Applicant is informed, that D3 discloses subject-matter that is comprised in the scope of the present set of claims.